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Cognitive Functioning at Age 10 Years Among Children Born Extremely Preterm: A Latent Profile Approach

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Abstract

Background—School-age children born extremely preterm (EP) are more likely than their term peers to have multiple neurocognitive limitations. We identify subgroups of EP children who share similar profiles on measures of IQ and executive function (EF), and describe the nature and prevalence of cognitive impairment in EP children.

Methods—Based on measures of IQ and EF, subgroups of EP children with common neurocognitive function are identified using latent profile analysis (LPA). Based on these subgroups, we describe the nature and prevalence of impairment in EP children, and examine associations between cognitive function, gestational age, and academic achievement. Classification of neurocognitive function using IQ and EF is compared to a standard classification based on IQ z-scores.

Results—LPA identified four neurocognitive profiles in EP children, with 34% of EP children classified normal, 41% low-normal, 17% moderately impaired, and 8% severely impaired. Impaired children exhibited global impairment across cognitive domains, while children in the low-normal group tended to have impaired inhibition relative to their reasoning and working memory skills.

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Conclusion—Within categories of EP children defined in terms of IQ, there is substantial variation in EF; thus both IQ and EF assessments are needed when describing school-age outcome of EP children.

Introduction

Despite reductions in mortality and major medical morbidities among children born extremely preterm (EP) (1), EP children continue to be at significant risk for moderate-to-severe neurocognitive impairment that persists through the school years into young adulthood (2). As a consequence of these impairments, children born preterm are at increased risk of poor school performance (3-5). Estimates of the prevalence of intellectual impairment, defined as a total intelligence quotient (IQ) below 70 (< -2 Z-scores below the mean), have ranged from 45% in a cohort of 11-year-olds born before 26 weeks (6) to 15% in a cohort of 16-year-olds with birth weight < 1250 grams and a mean gestational age of 28 weeks (7). Among children with subnormal, but not impaired IQ, overall function is likely determined by IQ and other neurocognitive abilities, especially executive function (8,9). Gaining a better understanding of the etiology of neurocognitive impairment and the antenatal and neonatal antecedents of unfavorable cognitive outcomes among EP children is a primary aim of epidemiological research on prematurity.

Existing studies of cognitive outcomes among individuals born EP illustrate several challenges to formulating an operational definition of cognitive impairment. Often, children are categorized as cognitively impaired based on IQ less than 70 (more than 2 standard deviations below the normative mean), both in epidemiological studies (6,7) and clinical trials (10,11). However, children born preterm exhibit impairment in virtually all domains of cognitive function (2), and cognitive deficits in EP children tend to co-occur (5,12,13). Evaluating each measurement domain for associations with antecedent factors or later outcomes results in multiple significance tests and difficulties in parceling the effects of highly correlated measures. Alternatively, summarizing a child's impairment based on their maximum impairment level across a set of measures or domains (6) fails to describe either the breadth of impairment or differences in patterns of impairment across measures. In fact, a recent systematic review found that no studies of risk factors for cognitive impairment among children born very preterm incorporated assessments of executive function into their measurements of outcome (14).

Latent profile analysis (LPA) operates by empirically identifying subgroups of children who share similar profiles on a set of measures. In this study, using LPA, we examine the nature and prevalence of cognitive functioning in EP children taking into account verbal and nonverbal IQ and executive functions. As a means of demonstrating content validity for this approach, we examine the association between cognitive profiles based on both IQ and EP at 10 years and lower gestational age, a risk factor for poorer cognitive outcomes (6,15). We also compare cognitive profiles based on IQ and EF to a standard classification based on IQ z-scores as predictors of academic achievement and the need for special education.

Methods

Participants

The ELGAN (Extremely Low Gestational Age Newborn) Study is a multicenter observational study of the risk of structural and functional neurologic disorders in EP children (16-18). During the years 2002-2004, women delivering before 28 weeks gestation in 11 cities in 5 states were asked to enroll in the study. 1249 mothers of 1506 infants consented to participate. Of 1200 EP infants who survived to age 2 years, the parents of 1102 (92%) consented to have their child participate in follow-up of developmental outcomes at age 2 years. Families of children with data on inflammatory biomarkers at birth (n=966), most of whom participated in the age 2 follow-up, were invited by mail and then phone to participate in the age 10 follow-up. Families of 889 of the 966 (92%) targeted children participated in the age 10 study. For 11 families, the parents participated in the follow-up interview but the child did not participate in the follow-up evaluation, and an additional 5 children were unable to undergo neurocognitive assessment at the visit. The remaining 873 children participated in the neurocognitive evaluation and are included in these analyses. Enrollment and consent procedures for this follow up study were approved by the institutional review boards of all participating institutions.

Measures

Assessments were selected to provide a broad overview of neurocognitive and academic function given the time constraints. This report focuses on two key indices of cognitive ability: general cognitive ability, or IQ, and executive function.

Verbal and nonverbal reasoning—General cognitive ability (or IQ) was assessed with the School-Age Differential Ability Scales–II (DAS-II) Verbal and Nonverbal Reasoning scales. The DAS has several advantages for characterizing the wide range of cognitive ability in a EP sample, including more sensitive basal items than the Wechsler and other IQ scales, and extended standard scores (down to 31) for lower-ability individuals. In addition, the DAS nonverbal reasoning subtests require minimal visual-spatial processing and fine motor dexterity allowing more accurate estimate of nonverbal reasoning in preterm children.

Executive function—Two subtests from the DAS-II and five subtests from the NEPSY-II were used to assess executive function. The DAS-II Recall of Digits Backward and Recall of Sequential Order subtests measured working memory. From the NEPSY-II, the Auditory Attention and Response Set subtests measured sustained attention, set-shifting and inhibition; the Inhibition-Inhibition and Inhibition-Switching subtests measured inhibition and set-shifting; and the Animal Sorting subtest measured concept generation and mental flexibility.

Academic achievement—The Wechsler Individual Achievement Test - III (WIAT - III) Word Reading and Numerical Operations subtests were used to assess children's basic reading and math skills. Whether a child had an individual education plan (IEP), repeated a grade, or was in a class for children with special needs was reported by the parent.

We defined impairment on any individual cognitive or academic achievement measure as a score two or more standard deviations below the normative mean.

Statistical Methods

LPA was used to identify subgroups of EP children with similar profiles of scores on 9 variables measuring verbal and nonverbal IQ (DAS-II Verbal and Nonverbal Reasoning scales), working memory (DAS-II Recall of Digits Backwards, Recall Sequential Order), concept generation and mental flexibility (NEPSY-II Animal Sorting), auditory attention and set switching (NEPSY-II Auditory Attention, Response Set), and simple inhibition and inhibition shifting (NEPSY-II Inhibition Inhibition and Inhibition Switching). LPA was conducted using Mplus 7.11 (19) which provides maximum likelihood estimation and includes children with missing data on some measures under the missing at random assumption. Successive LPA models were fit to the data, starting with a model including only one profile and increasing up to six profiles. To determine the optimal number of profiles, the fit of each model was examined through the Bayesian Information Criteria (BIC) (20), the sample-size adjusted Bayesian Information Criteria (SSABIC) (21) and the Lo-Mendell-Rubin adjusted likelihood ratio test (LMR) (22). For both the BIC and SSABIC lower values indicate better fit; for the LMR a significant result indicates that the model is a better fit than the model with one less profile. Entropy values were also used to determine the model with the optimal LPA solution. Entropy values range from 0 to 1. The closer the value is to 1, the better the separation of the profiles (23).

Children were categorized by their most likely latent profile for further analysis. A concern with categorizing based on the most likely profile is that it fails to account for potential misclassification (24). However, the impact of misclassification is small when entropy is high (greater than 0.80).

Children are also categorized using a standard classification based on IQ alone. DAS verbal and non-verbal IQ scores were converted to Z-scores (giving the IQ as standard deviations from the mean, by subtracting the normative mean of 100 and dividing by the normative standard deviation of 15) and then averaged. We refer to this averaged IQ Z-score as Z_{IQ} . Children are classified as having severely impaired, moderately impaired, or non-impaired IQ if their Z_{IQ} is -2 or below, between -2 and -1, or above -1.

Prevalences of the cognitive profiles are reported for the overall sample and by gestational age (categorized as 23-24, 25-26, and 27 weeks), with 95% confidence intervals (CI); the difference in the prevalences of cognitive profiles by gestational age was tested using the chi-square test. Analysis of variance followed by Scheffe's procedure was used to test for a difference among profile groups based on both IQ and EF on mean academic achievement, and chi-square analysis was used to test for the difference among profiles on the percent of children with an IEP, repeating a class, and in a special needs class. Comparison of academic achievement and educational needs across cognitive function profiles defined by LPA on both IQ and EF, for children with a specific Z_{IQ} categorization, were conducted through ANOVA and chi-square.

Twenty-four children in the sample had severe motor impairment or functional blindness that could invalidate their cognitive assessment. These children were included in the main analyses. In secondary analyses, the LPA was repeated excluding these children.

Results

Sample Description

Of the 873 participants, 17 (1.9%) had severe motor impairment (GMFCS = 5) and 7 (0.8%) had functional blindness (2 children had both severe motor impairment and functional blindness). Participants who were not able to obtain a basal score (because of cognitive impairment) on a given test, were assigned a floor score for that test. Of children with severe motor or visual impairment, 17 did not achieve basal scores on any test, and 2 obtained basal scores on some but not all measures. Of children without severe motor or visual impairment, 12 did not achieve basal scores on any test, and 9 obtained basal scores on only some tests. In summary, a total of 29 children were assigned floor scores on all tests, and 11 were assigned floor scores on some tests.

Of the 873 children in this sample, 21% were born at 23-24 weeks gestation, 45% at 25-26 weeks gestation, and 34% at 27 weeks gestation. 49% are girls. 63% of mothers identified as white, 26% as black, and 10% as Hispanic. 41% had a high school education or less, and 35% were eligible for government-provided medical care insurance at the time of her child's delivery.

Cognitive profiles based on Z_{IQ}

Sixty-six percent ($n=573$) of the sample had IQ in the non-impaired range with Z_{IQ} above -1, while 19% had moderately-impaired IQ with Z_{IQ} between -2 and -1) and 15% had severely impaired IQ with Z_{IQ} of -2 or below.

Cognitive profiles from latent profile analysis of IQ and EF

Based on the fit indices the four-profile model provides the best fit for the data, with substantial improvement over the three-profile model in AIC and BIC values, and no significant improvement in fit with a five-profile model based on the Lo-Mendell-Rubin test ($p=0.07$). The four-profile model provides good separation of the subgroups with an entropy value of 0.88.

Profiles and prevalence—The means and standard deviations (SDs) of the cognitive measures used in the LPA are plotted as SDs about the normative means in Figure 1 and given for each profile in Supplemental Table S1. 34% (CI 31%, 38%) of children had a “normal” cognitive functioning profile, which is characterized by mean scores within the normal range on all 9 cognitive and executive function measures. 41% (CI 38%, 45%) of children had cognitive function consistent with a “low-normal” profile. Mean values on the 9 tests for this group ranged from 0.5 SD below the norm (for IQ) to over one SD below the norm (for inhibition/set shifting). 17% (CI 14%, 19%) had a “moderately-impaired” profile, with means on the 9 measures between 1.5 and 2.5 SDs below normative values. 8% (CI 6%,

10%) of children exhibited a “severely-impaired” cognitive function profile, with means on the 9 measures approximately 3 to 4 SDs below normative values.

Excluding the 24 children with severe visual and motor impairments yielded very similar results on the LPA, with entropy of 0.88 for the four-profile model and $p=0.418$ for the Lo-Mendell-Rubin test showing no significant improvement with a five-profile model. 99% of children without visual or motor impairment fell into the same impairment profile for the LPAs on the full and restricted samples. For children without visual or motor impairment, 35%, 42%, 17%, and 6% were classified as having a normal, low-normal, moderately-impaired, and severely-impaired profile.

General vs. specific impairment—The percent of children with impairment (2 or more SDs below the norm) on one or more individual measures of IQ or EF varied prominently with profile assignment (Table 1). For example, 99% (CI 98%, 100%) of those with the normal and 96% (CI 94%, 98%) of those with the low-normal cognitive function profile had either no impairment or impairment in only one domain, while 65% (CI 57%, 73%) of those with the moderate impairment and 100% (CI 95%, 100%) of those with the severe impairment profile had both IQ and EF impairments. Children with moderate and severe impairment profiles exhibited global impairment, with high levels of impairment on all IQ and executive function measures. Children with the low-normal profile tended to have a relatively specific impairment or sets of impairment, largely with respect to executive function. For example, few of these children showed impairment on IQ or working memory measures, while 22% (CI 18%, 26%) showed impairment in sustained attention, 23% (CI 19%, 27%) in concept generation, and 46% (CI 41%, 51%) in inhibition.

Cognitive function profiles by gestational age—Gestational age ranged from 23 to 27 weeks in our sample. Children born at 23 - 24 weeks gestational age were most likely to have the severely impaired profile and least likely to have the normal profile (Table 2).

Comparison of cognitive function categorizations based on IQ and EF vs. Z_{IQ}

Of the 66% of EP children with Z_{IQ} above -1, roughly half (34% of the overall sample) were categorized as having normal cognitive function based on IQ and EF, and half (30% of the overall sample) as having low normal function (Table 3). Similarly, children with Z_{IQ} between -2 and -1 were roughly evenly divided into the low normal and moderately impaired profiles based on IQ and EF, and children with Z_{IQ} of -2 or below are roughly evenly divided between the moderately and severely impaired profiles based on IQ and EF.

Cognitive function profile and academic achievement—Children with the moderate and severely impaired profiles based on IQ and EF were more likely to have lower scores on academic achievement measures of literacy and math (Table 4). Children with the moderately-impaired cognitive function profile had mean WIAT-III achievement scores 1.5 to 2 standard deviations below the normative level, while children with the severely-impaired profile had mean WIAT-III achievement scores 3 standard deviations below the norms. The mean academic performance scores for children with the normal profile were at

or slightly above normative levels of achievement, while the scores for the low-normal profile children were just below the norm.

Among EP children with Z_{IQ} between -2 and -1, those with low normal profiles based on IQ and EF had significantly higher WIAT-III word reading and numerical operations scores than those with moderately impaired profiles (Table 4). Similarly, among children with Z_{IQ} of -2 or below, those with moderately impaired profiles based on IQ and EF had significantly higher achievement scores than those with severely impaired profiles based on IQ and EF.

Educational needs—Children with poorer cognitive function based on IQ and EF had more special needs at school (Table 5). The percent of children with an IEP increased from 28% among those with a normal profile to 52%, 88% and 99% among those with low normal, moderately impaired, and severely-impaired profiles. The percent enrolled in a special class increased from 3% among those with the normal profile to 49% and 93% among those with the moderately and severely-impaired profiles.

For children with Z_{IQ} between -2 and -1, the percent with an IEP was greater for those with a moderately impaired profile based on IQ and EF (83%) than for those with a low normal profile (65%, Table 5). For those with Z_{IQ} -2 or below, the percent in a special class was greater for those with a severely impaired profile on IQ and EF (93%) than for those with a moderately impaired profile (60%).

Discussion

Using latent profile analysis to summarize 9 measures of cognitive ability, we assigned 873 children into 4 distinct cognitive function subgroups. Three quarters of EP children had normal profiles (34% normal, 41% low-normal), while 17% had moderately-impaired and 8% severely-impaired profiles. As hypothesized, the percent of children in the moderately and severely impaired groups increased with decreasing gestational age at birth. Lending further support to the construct validity of these cognitive profiles, those with more impaired profiles scored lower on basic literacy and math skills and were more likely to have an IEP, repeat a grade, or be in a separate special class or program. Beyond these findings, the LPA results indicate that some EP children are globally impaired across cognitive domains while others have more specific impairment in executive function. EP children with the low-normal cognitive function profile were much more likely to show impairment in executive function than general reasoning ability, or IQ. However, EP children with the moderately or severely impaired profiles generally showed more global impairment in both IQ and executive function.

Characterizing cognitive function using measures of executive function in addition to IQ better discriminates the academic performance and educational needs of EP children. Given a child's IQ classification, children with more impaired profiles based on IQ and EF had lower academic performance and greater educational needs.

Our findings in extremely preterm children (born from 23 to 27 weeks gestation) agree in some respects, and disagree in others, with a study using LPA to classify moderately preterm children (born from 32 to 36 weeks gestation) by cognitive function at age 7 years (25).

Although our study used assessments of IQ, attention and executive control that were different from those used by Cserjesi and colleagues, both studies identified four profiles of cognitive functioning, and similar percentages of children falling into the highest functioning to lowest functioning profiles. However, children in the moderately preterm study were of generally higher cognitive ability than children in our EP sample. In particular, among moderately preterm children, mean IQ and attention scores in the two highest profiles were approximately half a SD above the norm and at the norm, respectively, while the two highest profiles for EP children corresponded to performance at the norm and roughly half a SD below the norm, respectively. The lowest functioning profile in the moderately preterm sample had means 1 to 2 SDs below the norm, while the lowest functioning profile in the ELGAN sample had means 3 or more SDs below the norm. These differences are consistent with prior findings (and findings from our EP sample) that severity of cognitive impairment increases with decreasing gestational age at birth (6,15,26).

Although the percent of children with the low-normal profile remained fairly constant for children born from 23 – 27 weeks gestation, the percent of children in the moderately and severely impaired groups increased as gestational age at delivery decreased, with an overall prevalence of 25%. In contrast, when we previously examined gestational age effects on IQ in the same cohort (26) impairment was inversely proportional to gestational age, but only 16% of children were categorized as moderate to severely impaired (two or more standard deviations below the normative mean) based on measures of IQ. Accordingly, we argue that IQ does not capture the full impact of cognitive function on outcome, and that the ability of LPA to summarize performance across a broader range of measures improves the ability to identify children at highest risk (8,9).

A strength of this study is that it is based on a large sample of preterm infants identified at birth, with measures of cognitive functioning that include verbal and nonverbal IQ, working memory, attention, set-shifting, inhibition, and mental flexibility. However, a limitation of our study is that other neurocognitive domains including visuospatial processing, language, and memory, are not included in our analyses. We do not know how impairment on these domains might have altered the number of profiles that might be identified by an LPA. Also, our LPA and the identified profiles are based on cognitive functioning scores, rather than on clinically defined impairment. Advantages to this approach are that it allows differentiation of profiles that represent lower but not impaired cognitive functioning, and that the identification of profiles does not depend on cut-off scores for impairment. A limitation is that our groups are not based on clinically defined impairment, although the associations we found between school achievement and cognitive function determined by the LPA suggest the results have clinical relevance.

We found that IQ alone does not fully capture cognitive function, and that considering measures of executive function improves the ability to identify impairment in EP children. 25% of 10 year olds born EP had moderate to severe impairment based on measures of IQ and EF. Among EP children who were less impaired, there was some evidence of differential impairment specifically in inhibitory control. Our classification of impairment showed the expected associations with gestational age, educational history, and academic achievement.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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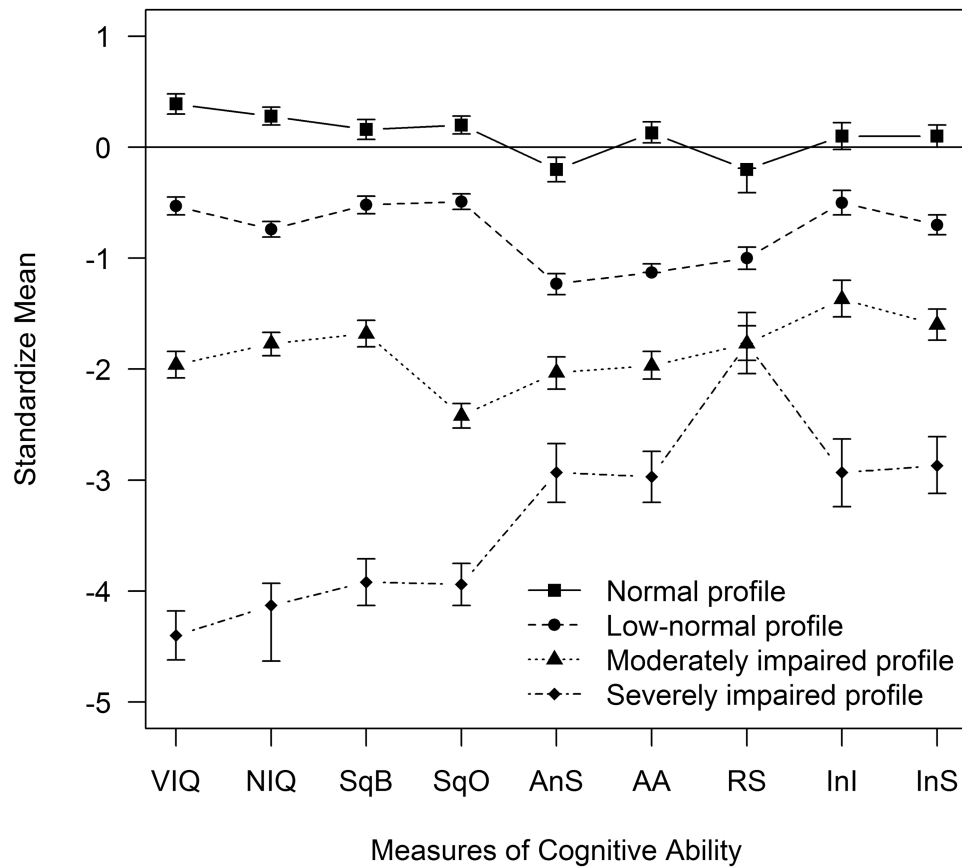


Figure 1.

Means of cognitive ability measures (in standard deviations from the norm) for the four LPA classes. Bars represent 95% confidence interval around the mean.

VIQ – DAS-II Verbal Reasoning, NIQ – DAS-II Nonverbal Reasoning, SqB – DAS-II Recall of Digits Backward, SqO – DAS-II Recall of Sequential Order, AnS – NEPSY-II Animal Sorting, AA - NEPSY-II Auditory Attention, RS - NEPSY-II Response Set, InI - NEPSY-II Inhibition-Inhibition, InS - NEPSY-II Inhibition-Switching

Table 1

Percent of children with 1 or more impairment^a on measures of verbal and nonverbal IQ and executive function, by cognitive function profile based on IQ and EF.

	<u>LPA Profile Based on IQ and EF</u>			
	Normal (n=299)	Low Normal (n=360)	Moderately Impaired (n=145)	Severely Impaired (n=69)
<u>Z-scores < -2</u>				
None	82	28	<1	0
IQ only	<1	3	0	0
EF only	18	66	34	0
Both IQ and EF	0	4	65	100

Table 2
Percent of children with each cognitive function profile based on IQ and EF, by gestational age

Gestational age	N	Cognitive Function Profile			
		Normal	Low Normal	Moderately Impaired	Severely Impaired
23-24 weeks	180	23	39	21	17
25-26 weeks	395	33	42	18	7
27 weeks	298	43	41	13	3

Distribution of cognitive profiles significantly differ by gestational age, chi-square $p < 0.001$

Table 3

Cognitive profile classification based on IQ and EF vs. based on IQ only. Percentages are percent of the overall sample.

	Profile Based on IQ and EF				
	Normal	Low Normal	Moderately Impaired	Severely Impaired	Overall
Classification based on IQ only					
$Z_{IQ} > -1$	n=298 34.1%	n=264 30.2%	n=11 1.9%	0	n=573 65.6%
$-2 < Z_{IQ} \leq -1$	1 0.6	n=94 10.8%	n=71 8.1%	0	n=166 19.0%
$Z_{IQ} \leq -2$	0	n=2 0.2%	n=63 7.2%	n=69 7.9%	n=134 15.4%
Overall	n=299 34.2%	n=360 41.2%	n=145 16.6%	n=69 7.9%	n=873

Table 4
Mean and standard deviation of WIAT Word Reading (top row in each cell) and Numerical Operations scores, by cognitive function profiles based on IQ and EF, and classification based on IQ only

Classification based on IQ Only	Profile based on IQ and EF			
	Normal	Low Normal	Moderately Impaired	Severely Impaired
Overall ^a	107.8 (11.8)	94.4 (13.2)	77.9 (14.4)	51.1 (15.1)
	103.2 (12.3)	90.7 (11.7)	71.8 (14.3)	44.4 (10.0)
	n=299	n=360	n=145	n=69
$Z_{IQ} > -1^b$	107.8 (11.7)	96.4 (12.7)	88.5 (11.4)	0
	103.2 (12.3)	92.7 (11.5)	87.5 (13.0)	
	n=298	n=264	n=11	
$-2 < Z_{IQ} \leq -1^a$	---	89.0 (13.2)	81.0 (15.4)	0
	---	85.7 (10.4)	74.4 (13.8)	
	n=1	n=94	n=71	
$Z_{IQ} \leq -2^a$	0	---	72.6 (11.4)	51.1 (15.1)
		---	66.1 (12.1)	44.4 (10.0)
		n=2	n=63	n=69

^a p<0.001 from ANOVA comparing means across the row, for both WIAT Word Reading and Numerical Operations, all pairwise comparisons p<0.001 from Scheffe's procedure

^b p<0.001 from ANOVA comparing LPA profiles of Normal, Low Normal, for both WIAT Word Reading and Numerical Operations

Table 5
Percent of children had an IEP, repeated a grade, special class, by cognitive function profiles based on IQ and EF, and on IQ only

Classification by IQ Only	Classification by IQ and EF			
	Normal	Low Normal	Moderately Impaired	Severely Impaired
Overall ^a	83 (28%)	188 (52%)	128 (88%)	68 (99%)
	22 (7%)	75 (21%)	56 (39%)	9 (13%)
	10 (3%)	36 (10%)	71 (49%)	64 (93%)
	n=299	n=360	n=145	n=69
$Z_{IQ} > -1$ ^b	83 (28%)	132 (48%)	8 (64%)	0
	22 (7%)	53 (20%)	3 (27%)	
	10 (3%)	18 (6%)	4 (27%)	
	n=298	n=264	n=11	
$-2 < Z_{IQ} < -1$ ^a	n=1	55 (64%)	61 (83%)	0
		22 (24%)	34 (46%)	
		18 (20%)	30 (42%)	
		n=94	n=71	
$Z_{IQ} < -2$ ^c	0	n=2	59 (98%)	68 (99%)
			19 (32%)	9 (13%)
			37 (60%)	64 (93%)
			n=63	n=69

^a p<0.001 comparing percentages across the row for IEP, repeat a grade, and special class via chi-square test

^b p<0.01 comparing percentages across the row for IEP, repeat a grade, and special class via chi-square test

^c p=0.921 for IEP, p=0.011 for repeat grade, p<0.001 for special class comparing percentages across the row via chi-square test